

REMARKS/ARGUMENTS

Claims 16-26 are active. Minor edits have been made to improve the clarity of the claims. Claim 16 has been revised to refer to an isolated pretreated chemiluminescence enhancer. Support for this phrase is found *inter alia* on pages 13-14 which describe treatment (pretreatment prior to use) and isolation of the pretreated enhancer from the oxidizing or reducing agent (also prior to use), e.g., by dialysis. New Claim 26 finds support in the specification on page 12, lines 8-12. No new matter has been added.

Aspects of the Invention

An object of the invention is to provide a superior chemiluminescence enhancer by treating a known chemiluminescence enhancer with an oxidizing or reducing agent. The oxidizing or reducing agent is used to \*treat\* a known chemiluminescence enhancer and the \*treated chemiluminescence enhancer\* is added to a liquid medium which contains an appropriate chemiluminescent substrate. That is, the oxidizing or reducing agent used to pretreat the enhancer is not present in the liquid medium for the chemiluminescent measurement.

The invention is directed to a method of producing chemiluminescence in a solid phase immunoassay. The method comprises contacting at least one antigen or/and an antibody immobilized onto fine solid carriers dispersed in a liquid medium with a chemiluminescence substrate comprising at least one dioxetane, an enzyme for performing chemiluminescence, and a \*treated\* chemiluminescence enhancer comprising a water soluble macromolecular quaternary ammonium salt, a water soluble macromolecular sulfonium salt or a water soluble macromolecular quaternary phosphonium salt each of which has been treated with an oxidizing agent or a reducing agent.

The \*treated\* chemiluminescence enhancer of the present invention provides for improved dispersibility of fine solid carriers in a chemiluminescence reaction compared to reactions where a conventional chemiluminescence enhancer is used. Enhancement of chemiluminescence and within-run reproducibility (CV value) is achieved by the invention and more precise quantification becomes possible as described by Examples 1-7 of the specification.

Rejection—35 U.S.C. §103

Claims 16-25 were rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al., U.S. Patent No. 5,753,436, in view of Akhavan-Tafti et al., U.S. Patent No. 6,045,727.

While Bronstein et al. (US 5,753,436) disclose a “chemiluminescence enhancer”, this document describes a quaternary ammonium, phosphonium or sulfonium salt chemiluminescence enhancer, which is different from a chemiluminescence enhancer which has been treated with an oxidizing agent or a reducing agent as required by the present invention.

There is no suggestion or reasonable expectation of success for the superior properties of the chemiluminescence enhancers of the invention in Bronstein. These superior properties are demonstrated by the comparisons between a chemiluminescence enhancer of Bronstein et al. and a chemiluminescence enhancer of the present invention are described in Examples 1-7 of the present specification. For example, table 1 on page 14 of the present specification shows that, the treated TBQ groups corresponding to a chemiluminescence enhancer of the present invention increased the luminescence and enhanced within-run reproducibility (CV value), that is, led to the enhancement and stabilization of luminescence as compared to the untreated TBQ corresponding to a chemiluminescence enhancer of Bronstein et al.

As shown, the effects of the present invention in chemiluminescence method using the fine solid carriers are extremely superior to that of the method of Bronstein et al.

Akhaven-Tafti et al. was cited as teaching a chemiluminescence method which includes "the addition of an effective amount of a background reducing agent (oxidizing or reducing) to the chemiluminescent composition". Independent Claim 16 now clearly specifies that the pretreated chemiluminescence enhancer is isolated from the oxidizing or reducing agent prior to its use. On the other hand, Akhaven-Tafti adds the oxidizing or reducing agent (e.g., sulfite salts) to the assay mixture and these salts are present in the composition during the chemiluminescence measurement.

Moreover, as detailed below, there is no suggestion in this document for the present invention, this document provides no motivation for combining its teachings with those of the primary reference because it employs different reagents and uses certain components for different reasons. Moreover, there is no reasonable expectation of success for the superior results obtained by the present inventions in Akhaven-Tafti et al.

Comparisons of the components of a conventional (untreated) reagent for chemiluminescence described in Akhaven-Tafti et al. and a \*treated\* reagent of the present invention (Claim 16) is shown in the following table:

| Constituent  | Claim 16 of the present invention   | Akhaven-Tafti et al. (Column 21, line 45...)  |
|--|---|---|
| Chemiluminescent substrate   | dioxetane   | Compound of formula I-V (Not dioxetane compounds)   |
| Chemiluminescence enhancer   | A water soluble macromolecular quaternary ammonium salt, a water soluble macromolecular sulfonium salt or a water soluble macromolecular quaternary phosphonium salt chemiluminescence enhancer treated with an oxidizing agent or a reducing agent | Anionic surfactant (SDS) and non-ionic surfactant (Tween 20)<br><br>(SDS is not a water soluble <u>macromolecular sulfonium salt</u> .) |
| Compounds having oxidation/reduction potential suitable for causing an increase in chemiluminescence | -   | Cationic aromatic compound (CAC): cyan dyes, thiacyanine dyes, carbocyanine dyes...   |
| Background reducing agents   | -   | Sulfite salts (lithium sulfite, sodium sulfite, potassium sulfite)  |
| Effects  |   |   |
|  | Improvement in dispersibility of fine solid carriers and increase in within-run reproducibility (CV value)  | Sulfite salts prevent the accumulation of background chemiluminescence and reduce the background amount.                                |

Akhaven-Tafti et al. disclose a conventional chemiluminescence enhancer comprising a surfactant for the addition to a chemiluminescent substrate of formula I-V (Akhaven-Tafti, column 14, lines 49-67 and column 15, lines 1-36). Also it is disclosed that when anionic surfactants or nonionic surfactants are used as a chemiluminescence enhancer, CAC suitable for causing an increase in chemiluminescence and sulfite salts as a reagent for reducing background amount are further added to the chemiluminescent substrate mentioned at column 21, lines 45-63.

In Akhaven-Tafti et al., sulfite salts are added to chemiluminescence substrate as a background reducing agent as mentioned at column 21, lines 45-63, while in the present invention, sulfite salts are used to pretreat a chemiluminescence enhancer.

The Office asserts that it would have been obvious to one of ordinary skill in the art to include a background reducing agent in the method of Bronstein et al. as taught by Akhaven-Tafti et al. However, Akhaven-Tafti et al. does not disclose or suggest the pretreatment of a chemiluminescence enhancer with an oxidizing agent or a reducing agent.

In addition, the chemiluminescence enhancer of Akhaven-Tafti et al. is not used for pretreatment of a chemiluminescent substrate comprising dioxetane. As can be seen from the above table, a constitution of chemiluminescence enhancer and constituent of reagents, etc. used in chemiluminescence measurements of the present invention is completely different from those of Akhaven-Tafti et al.

Furthermore, the cited prior art provides no motivation for combining the teachings of Bronstein et al. and Akhaven-Tafti et al. The effect of Akhaven-Tafti et al. is to prevent accumulation of background chemiluminescence, while the effect of the present invention is to improve dispersibility of fine solid carriers and increase within-run reproducibility (CV value) at a time of measurement. Accordingly, the cited prior art does not suggest or provide a reasonable expectation of success for the present invention and, therefore, the Applicants respectfully request that this rejection be withdrawn.

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CONCLUSION

In view of the remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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